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APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO.
08/469,641	06/06/95	HU	~~225800-163~~

EXAMINER

HM11/0522

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ART UNIT	PAPER NUMBER
~~1646~~	20

DATE MAILED: 05/22/98

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☒ Responsive to communication(s) filed on 3/11/98

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or ~~thirty days,~~ whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 41-73 is/are pending in the application.
Of the above, claim(s) _____ is/are withdrawn from consideration.
☐ Claim(s) _____ is/are allowed.
☒ Claim(s) 41-73 is/are rejected.
☐ Claim(s) _____ is/are objected to.
☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.
☐ The specification is objected to by the Examiner.
☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.
☐ received in Application No. (Series Code/Serial Number) _____.
☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of Reference Cited, PTO-892
☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____
☐ Interview Summary, PTO-413
☐ Notice of Draftperson's Patent Drawing Review, PTO-948
☐ Notice of Informal Patent Application, PTO-152

--SEE OFFICE ACTION ON THE FOLLOWING PAGES--

* U.S. GPO: 1996-404-496/40517

DETAILED ACTION

Response to Amendment

1. Claims 24 and 31-36 have been amended and claim 40 has been added in the amendment of 07 July 1997. Claims 21-40 are currently pending and under consideration in the instant application.

2. Any objection or rejection of record which is not expressly repeated in this action has been overcome by Applicant's response and withdrawn.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Response to Arguments

4. Applicant's arguments filed 07 July 1997 have been fully considered but they are not persuasive.

Sequence Compliance

5. Applicant's new CRF and paper copy of the Sequence Listing have been received. However, the CRF of the Sequence Listing contained errors which were detected by STIC when processing the CRF diskette. Attached to this Office action is a marked-up copy of the Raw Sequence Listing which details the errors that are present in the CRF of the Sequence Listing. Also included with this Office action is a Notice to Comply which details what is required at this

time to place the instant application in compliance with the Sequence Rules. Correction is required.

Claim Rejections - 35 USC § 112

6. Claims 31-33 stand rejected (and newly added claim 40 is rejected) under 35 U.S.C. 112, first paragraph, because the specification, while being enabling methods of making a polypeptide by expressing the DNA which encodes the polypeptide of SEQ ID NO:2, does not reasonably provide enablement for methods of making a polypeptide by expressing polynucleotides having 95% identity to polynucleotides which encode a polypeptide for the reasons of record as applied to claims 31-33 in paper #8. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Applicant has first argued that claims now include a limitation that "the polypeptide have the ability to stimulate the proliferation of human endothelial cells", that such activity could be assayed for, that such an assay would be routine in the art and that only the production of active polypeptides is claimed. This argument is not found persuasive because although an activity limitation has been added, the claim from which claims 31-33 ultimately depend (claim 21) does not require the polynucleotide to encode a protein. Therefore, using a polynucleotide which is 95% identical to a polynucleotide which encodes a protein of SEQ ID NO:2 will not necessarily result in a polynucleotide which either encodes a protein or if it does encode a protein, may have no recognizable similarity to the protein of SEQ ID NO:2. This is because a polynucleotide which

is 95% identical includes polynucleotides which have frame shifts, stop codons, etc. and therefore it is not predictable which of those polynucleotides which are 95% identical will encode a protein OR will encode a protein which has a biological activity of the disclosed protein of the instant application. In the instant case, it would not be routine to simply screen and test those polynucleotides which meet the structural limitations of the claim (i.e. 95% identity) and then determine which of those also meet the functional limitations of the claim (i.e. have the ability to stimulate the proliferation of human endothelial cells).

The issue here is the breadth of the claims in light of the predictability of the art as determined by the number of working examples, the skill level of the artisan and the guidance presented in the instant specification and the prior art of record. This position is consistent with the decisions in *In re Fisher*, 427 F.2d 833, 166 USPQ 18 (CCPA 1970) and Amgen Inc. v. Chugai Pharmaceuticals Co. Ltd., 13 USPQ2d, 1737 (1990) and In re Wands, 8 USPQ2d, 1400 (CAFC 1988). The factors to be considered in determining whether a disclosure would require undue experimentation include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and, (8) the breadth of the claims, as indicated in the previous Office action. All of this factors were addressed in the initial rejection. Applicant's argument that the standard is that of making a subject protein and testing to see if it retains the

desired biological activity is a position that has been routinely dismissed by the courts, as shown by those decisions cited above.

Further, In re Wands determined that the repetition of work which was disclosed in a patent application as producing a composition containing an antibody, which is a naturally occurring compound, did not constitute undue experimentation even if the antibody produced thereby was not identical to those that were disclosed in that application. The instant claims are not limited to naturally occurring compounds and the instant specification does not provide a description of a repeatable process of producing a vascular endothelial growth factor whose amino acid deviates from one disclosed sequence by as much as 15% (which is encompassed by a polynucleotide which is 95% identical) when taking into consideration only variants which have substitutions. (It should be noted that variation in the polynucleotide sequence of 5%, which also encompasses insertions and deletions, could result in a polynucleotide which may not even encode a protein or result in a protein with much greater than 15% variation.) To practice the instant invention in a manner consistent with the breadth of the claims would not require just a repetition of the work that is described in the instant application but a substantial inventive contribution on the part of a practitioner which would involve the determination of those amino acid residues in the vascular endothelial growth factor which are required for the functional and structural integrity of the protein. It is this additional characterization of the protein that is required in order to obtain the functional and structural data needed to permit one to produce a protein which meets both the structural and functional requirements of the instant claims that constitutes undue

experimentation. To argue that one can make material embodiments of the invention and then test for those that work in the manner disclosed or that the instant claims only encompass the working embodiments is judicially unsound. Unless one has a reasonable expectation that any one material embodiment of the claimed invention would be more likely than not to function in the manner disclosed or the instant specification provides sufficient guidance to permit one to identify those embodiments which are more likely to work that not without actually making and testing them then the instant application does not support the breadth of the claims. In the instant case it is highly improbable that any protein having 85% amino acid sequence identity (when only considering nucleotide variation which results in "substitutions" of amino acids) to the disclosed protein will more likely than not perform in the manner disclosed and the instant specification does not provide the guidance needed to predictably alter the sequence with any reasonable expectation that the resulting protein will have the biological activity of the disclosed vascular endothelial growth factor.

Applicant also argues that "starting material polynucleotides for transforming a host or otherwise expressing the claimed polypeptides are the polynucleotides sequences that are admitted as being allowable" (see page 8 of response) and that standard assays exist for determining activity. These arguments appear to assert that since the starting materials are allowable, then the methods of using the starting materials should also be allowable. These arguments are not only found not to be persuasive, they also do not appear to have a statutory basis and Applicant is invited to provide that statutory basis. It appears that Applicant is alluding

to the decisions in *In re Ochiai* 37 USPQ2d 1127 (Fed. Cir. 1995) and *In re Brouwer* 37 USPQ2d 1663 (Fed. Cir. 1996). However, the issue was not one of an allowable starting material making the method allowable, but rather if a starting material was found to be **novel**, then a method using that starting material would also be **novel**. In the instant application, the issue at hand is one of enablement and not novelty (which is why a 102 rejection does not appear in the instant application). Furthermore, the argument regarding making and testing polypeptide variants has been addressed above. Therefore, Applicant's arguments are not persuasive and the rejection is maintained.

Conclusion

7. Claims 21-30 and 34-49 are allowable.

8. Claims 31-33 and 40 are rejected.

9. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for response to this final action is set to expire THREE MONTHS from the date of this action. In the event a first response is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37

CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event will the statutory period for response expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christine Saoud, Ph.D., whose telephone number is (703) 305-7519. The examiner can normally be reached on Monday to Thursday from 8AM to 4PM. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Stephen Walsh, can be reached on (703) 308-2957. The fax phone number for this Group is (703) 308-0294.

Official papers filed by fax should be directed to (703) 308-4242. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294.

Communications via Internet e-mail regarding this application, other than those under 35 U.S.C. 132 or which otherwise require a signature, may be used by the applicant and should be addressed to **[stephen.walsh@uspto.gov]**.

All Internet e-mail communications will be made of record in the application file. PTO employees do not engage in Internet communications where there exists a possibility that sensitive information could be identified or exchanged unless the record includes a properly signed express waiver of the confidentiality requirements of 35 U.S.C. 122. This is more clearly set forth in the Interim Internet Usage Policy published in the Official Gazette of the Patent and Trademark on February 25, 1997 at 1195 OG 89.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Christine Saoud, Ph.D.
September 9, 1997

JOHN ULM
PRIMARY EXAMINER
GROUP 1800